2,177,021) and Bellini et al. (EP 612,528) in view of the acknowledged prior art and Martindale The Extra Pharmacopoeia.

In traversal of this rejection, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness because the cited references, alone or in combination, do not teach or suggest the invention of the present claims or the desirability of the claimed invention. In support of this rejection, the Examiner states that:

> Harber et al. disclose the use of a "non-toxic iron-chelation substance" (claim 1) such as "non-protein iron-chelator" (page 1, lines 35-39) in peritoneal dialysate solutions to prevent peritonitis (page 1, lines 1-42). Concentration of the iron chelator is from 5 to 50 μM, which is approximately 27.9 to 279 μg/dl iron (page 1, lines 37-39). Ferric chloride is disclosed as one specific example of a non-protein iron-chelator, and its exemplified concentration is 10 μM, which is approximately 57.8 μg/dl iron (page 1, lines 45-51).

The Examiner's assertions quoted above include a number of errors that are evident upon careful inspection of the cited reference. In particular, Applicant submits that the Examiner has misinterpreted the meaning of the term "iron-chelation substance" as used in Harber et al. and has misinterpreted how ferric chloride is used in the Harber et al. experiment. The statement in the Action that a 5 to 50 μM concentration of the iron chelator is approximately 27.9 to 279 μg/dl iron improperly assumes that the iron-chelation substance includes iron, which is inconsistent with the clear meaning of the Harber et al. reference. Close inspection of Harber et al. reveals that the term "iron-chelation substance" does not refer to a composition including iron, but rather refers to a substance that forms a coordination compound with iron when it comes into contact therewith, i.e., that irreversibly binds free iron. Thus, a peritoneal dialysis fluid described by Harber et al. does not include iron, but rather includes a substance that chelates, or binds, iron. In keeping with the stated purpose of the iron-chelation substance, i.e., to remove iron from peritoneal dialysis fluid, a dialysate including an iron-chelation substance as described in Harber

et al. does not include iron, but instead functions when used for peritoneal dialysis to remove iron from the patient that enters the fluid during dialysis exchange.

The Harber et al. reference is specifically addressed to the problem of bacterial growth in peritoneal fluid resulting in peritonitis. Harber et al. hypothesized that, because "bacteria require iron as a nutrient for growth," bacterial growth would be prevented by chelating (i.e., irreversibly binding) any iron that may be present. As such, Harber et al. describe a peritoneal dialysis fluid that includes an iron-chelation substance to irreversibly bind any iron that makes its way into the fluid before or during dialysis exchange.

The experimental section beginning at page 1, line 44 of Harber et al. describes a test for this hypothesis in which peritoneal dialysis effluent (i.e., a fluid recovered from a patient's peritoneal cavity following a period of residence and dialysis exchange) was artificially supplemented with iron (in the form of ferric chloride or haemoglobin). Transferrin (an iron-chelation substance) was also added to some test samples in various concentrations. Test samples were then inoculated with bacteria and bacterial growth was observed in samples with and without transferrin present. The results showed that: "Transferrin strongly inhibited the growth of all four bacterial [sic] strains in PD effluent supplemented with ferric chloride, and also produced a significant suppression of bacterial growth rate in PD effluent supplemented with haemoglobin." (Harber et al., page 1, lines 63-67). In view of these results, Harber et al. propose a peritoneal dialysis fluid that includes an iron-chelator to bind any iron that makes its way into the peritoneal dialysis fluid before or during dialysis. Again, the iron-chelation substance included in a peritoneal dialysis fluid described by Harber et al. does not include iron, but rather is an iron-binding molecule that removes iron from the patient during dialysis.

In view of the above, the Examiner's statement that ferric chloride is "one specific example of a non-protein iron-chelator" is incorrect. As discussed above, ferric chloride is used in the Harber et al. reference only as an additive to a PD effluent, and only for artificially increasing the iron content of the effluent to test the effect of iron on bacterial growth and to test the effect of an iron-chelation substance for removing iron to prevent bacterial growth. Ferric chloride is in fact not an iron chelation substance, and is not identified as such in Harber et al.

Applicant would again emphasize the fact that the fluid used in the experiments set forth in Harber et al. is not a peritoneal dialysate, but is a peritoneal dialysis effluent, i.e., a fluid that has been recovered from a patient's peritoneal cavity following dialysis. A person of ordinary skill in the art will readily recognize that a peritoneal dialysis effluent, which is a fluid resulting after an exchange occurs between a peritoneal dialysate and a patient's blood, includes waste products, such as urea, creatinine and the like, and has a different overall composition than a dialysate, including different proportions of electrolytes. Indeed, a person of ordinary skill in the art would readily recognize that a peritoneal dialysis effluent does not include electrolytes "proportioned for dialysis of a patient" as recited in claims 24-29, 31-37, 39-41, 44 and 64-66 of the present application, as amended. Furthermore, claims 46-63 of the present application are directed to methods and compositions relating to more concentrated electrolyte and iron complex compositions commonly referred to as "dialysate concentrates." Because Harber et al. do not teach or suggest using a peritoneal dialysis fluid that includes iron, a person of ordinary skill in the art would find no motivation therein to make or use a dialysate concentrate that includes an iron complex as recited in these claims.

In view of the Examiner's misinterpretation of Harber et al., Applicant submits that the obviousness rejection is improper, and that no *prima facie* case of obviousness has been made.

A person of ordinary skill in the art would find no motivation in the cited references to remove the iron-chelation substance in the peritoneal dialysis fluid of Harber et al. and replace it with an iron complex of the composition recited in the pending claims of the present application.

Furthermore, in describing methods and compositions for removing iron from a peritoneal dialysis fluid and ultimately from a patient, Harber et al. teaches away from the present invention. Harber et al. teaches that iron should be removed from a peritoneal fluid to inhibit bacterial growth. This teaches directly away from the present invention, which recites a dialysate composition that includes an iron complex. Prior to the present invention, there was no teaching, suggestion or motivation to incorporate iron complexes into a dialysate as described in the present application to achieve iron delivery during dialysis, and the prior art, including Harber et al., teaches away from such incorporation.

Also, the modification proposed by the Examiner would render the peritoneal dialysis fluid described in Harber et al. unsatisfactory for its intended purpose, which is to eliminate iron from the fluid to prevent bacterial growth. Adding an iron complex as recited in the present claims to the Harber et al. fluid would "use up" at least a portion , and possibly all, of the iron-chelation substance prior to infusion into the patient, impairing or eliminating its ability to capture iron during residence in the peritoneal cavity. Replacement of the iron-chelation substance in the Harber et al. fluid with an iron complex as recited in the present claims would also render the Harber et al. fluid unsuitable for its intended purpose.

Turning now to the Bellini et al. reference, Applicant again submits that Bellini et al. cannot be cited as teaching or suggesting a dialysate formulation that contains ferrous gluconate because Bellini et al. would not motivate a person of ordinary skill in the art to include ferrous gluconate in a dialysate. Bellini et al. discloses "solutions for peritoneal dialysis that contain an

osmotic substance with is an alternative to glucose." (Col. 1, lines 1-3). More specifically, Bellini et al. disclose "a peritoneal dialysis solution ...characterized in that it comprises an osmotic substance chosen among gluconic acid and its pharmaceutically acceptable salts." (Col. 2, lines 30-34). Although Bellini et al. separately recites a list of known gluconic acid salts and the list includes iron gluconate, this reference does not teach or enable a peritoneal dialysis protocol using a dialysate including ferrous gluconate, and would not motivate a person of ordinary skill in the art to include iron gluconate in a dialysate.

As Applicant has asserted in response to a previous Office Action, if iron gluconate were selected as the gluconic acid salt in Bellini et al., as suggested by the Examiner, the dialysate would include from 10 g/l up to 50 g/l of iron gluconate, which would equal from about 91,000 to about 455,000 μg/dl of iron in the peritoneal dialysate. While the Bellini et al. dialysate may have good osmotic properties by virtue of a gluconic acid salt, Applicant submits that a person of ordinary skill in the art would not read Bellini et al. as teaching or suggesting the inclusion of ferrous gluconate in a dialysate. Rather, a person of ordinary skill in the art would dismiss any notion of including ferrous gluconate as the source of the gluconate salt, concluding that a peritoneal dialysate including ferrous gluconate, especially from about 91,000 to about 455,000 μg/dl of iron from ferrous gluconate, would be toxic. The lower end of this range is a concentration of iron that is more than 300 times greater than the iron concentrations in dialysate concentrates described and claimed in the present application. In addition to the fact that Bellini et al. would not motivate a person of ordinary skill in the art to include ferrous gluconate in a peritoneal dialysis fluid, Applicant further submits that no suggestion or motivation exists in Bellini et al. or any other prior art of record to make or use a dialysate including an iron complex "having a concentration in the water to provide an iron concentration of from about 1 to about

250 μg/dl" or a dialysate concentrate including electrolytes and an iron complex with "concentrations in the water whereby the composition is effective for dilution to provide a dialysate having ... an iron concentration of from about 1 to about 250 μg/dl" as recited in the pending claims. Irrespective of whether or not the list of known gluconic acid salts in Bellini et al. constitutes a "laundry list," Applicant maintains that a person of ordinary skill in the art would not be motivated by Bellini et al. to include ferrous gluconate in a dialysate.

It appears that the Examiner is attempting to assert that such a motivation arises from the knowledge that dialysis patients commonly require iron supplementation; however, Applicant submits that this knowledge does not supply the missing motivation because it provides no motivation to deliver iron to a patient using compositions as recited in the pending claims. The prior art is devoid of any teaching or suggestion to make or use a composition as recited in the pending claims, including electrolytes and an iron complex selected in accordance with the invention in the recited proportions. Applicant therefore respectfully submits that the above-stated rejection is overcome and respectfully requests withdrawal thereof.

It is believed that the above remarks overcome all rejections; however, it is worthy of note that additional reasons for the patentability of a number of claims are believed to exist. For example, the patentability of a number of dependent claims are premised herein, for purposes of expedience, upon the patentability of the independent claims from which they directly or indirectly depend. It is understood, however that the reasons for patentability provided above are not intended to be exhaustive of the bases for patentability, but are simply provided to overcome the rejections made in the outstanding Office Action in the most expedient fashion. The pending claims include features in addition to those explicitly discussed above, and Applicant submits

that the combinations are patentably distinct from the prior art for additional reasons not discussed herein.

CLOSING

In view of the above, Applicant respectfully submits that the present application, as amended and including pending claims 24-29, 31-37, 39-41, 44 and 46-66, is in condition for allowance. Action to that end is respectfully requested. If there are any remaining issues that can be addressed telephonically, the Examiner is invited to contact the undersigned to discuss the same.

Attached hereto is one page which presents a marked up version of the changes made to this application by the current amendment. This attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

A check in the amount of $445.00 is enclosed for a three-month extension of time. No additional fees are believed to be necessary, however, should any fees be deemed required, please charge such fees to Deposit Account No. 23-3030, but not to include any payment of issue fees.

Respectfully submitted,

By _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claims 32 and 40 were amended as follows:

32. (Thrice Amended) A method for making an aqueous composition useful as a dialysate, comprising, dissolving into water (i) a plurality of electrolytes in an amount effective to provide an electrolyte concentration in the water of from about 223 mEq/L to about 323 mEq/L, the electrolytes proportioned for dialysis of a patient and (ii) an iron complex comprising one or more divalent or trivalent iron ions and one or more anions and having a molecular weight of less than about 50,000 in an amount effective to provide an iron concentration in the water of from about 1 to about 250 μg/dl, to provide an aqueous composition.

40. (Twice Amended) A method for making an aqueous composition useful as a dialysate, comprising:

providing a first aqueous solution of electrolytes, the electrolytes having a concentration in the solution of from about 223 mEq/L to about 323 mEq/L and the electrolytes being proportioned for dialysis of a patient; and

introducing into the first solution an iron complex comprising one or more divalent or trivalent iron ions and one or more anions and having a molecular weight of less than about 50,000, to provide a second aqueous solution useful as a dialysate, the second aqueous solution having an iron concentration of from about 1 to about 250 μg/dl.